A SYSTEMATIC REVIEW AND META-ANALYSIS OF ANTIBIOTIC RESISTANCE PATTERN IN INDIA - "ARE WE LOOSING THE BATTLE AGAINST THE BUG?"

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ABSTRACT
More lives are being lost to even non-life threatening illnesses such as typhoid and common chest infections such as pneumonia as these are becoming harder to treat due to antibiotic resistance.[1] India has made a promising start by adopting the National Action Plan on AMR (2017-21) in April of 2017. The bottleneck is the available data in the AMR does not include daily defined doses of antibiotics and drug resistance index.[2] The objectives of this study are to conduct a systematic review and metanalysis of the consumption of selected antibiotics with respect to daily defined dose, resistance pattern of selected microorganisms, and the drug resistance index at country level during the last decade. Electronic search in PubMed/MEDLINE and Google Scholar was used to find published literatures using keywords antibiotic resistance, India and Human. Titles and abstracts were initially screened for eligibility.[3] The full texts of articles judged to be eligible were reviewed if they meet the inclusion criteria. The electronic searches identified 6749 articles of which 62 were found eligible. The resistance index in the year 2009 79% and in 2015 was 71%. A total 8 bacterial isolates were selected according to the list provided by WHO and the resistance pattern of all 8 isolates of bacteria were discouraging.[4] The change from being susceptible to being resistant is drastic in the last decade with 95% CI (16.6–41.7). Appropriate antibiotic use should be ensured by prohibiting over-the-counter sale of antibiotics and strengthening antimicrobial stewardship.[5] The urgency at the policy level needs to translate into action on the ground, which won't happen until the healthcare, pharmaceutical and livestock sector is better regulated.[6]

KEYWORDS: Antibiotic resistance, Resistance pattern, Resistance index, WHO, Antimicrobial stewardship.

INTRODUCTION
The indiscriminate use of antibiotics leading to drug resistance is the new challenge the whole medical fraternity is grappling with.[7] More lives are being lost to even non-life threatening illnesses such as typhoid and common chest infections such as pneumonia, as these are becoming harder to treat due to antibiotic resistance.[8]

Aim and Objective
The objectives of this study are to conduct a systematic review and Metaanalysis of the consumption of selected antibiotics with respect to daily defined dose, resistance pattern of selected microorganisms, and the drug resistance index at country level during the last decade.

METHODOLOGY
Electronic search in PubMed/MEDLINE and Google Scholar was used to find published literature with reference lists of relevant articles were searched manually using keywords antibiotic resistance, India and Human.[9] Titles and abstracts were initially screened for eligibility. The full texts of articles judged to be eligible were reviewed if they meet the inclusion criteria.[10] Data were extracted on important variables like the sample size, region of the study, the inappropriate antibiotic use, bacterial detection rate, multidrug resistance pattern, and more other variables.[11] Microsoft Excel was used for data extraction. Quantitative analysis was performed using SPSS version 21. The electronic searches identified 6749 articles of which 62 were found eligible.[12]

WHO priority pathogens list for R&D of new antibiotics Priority 1: CRITICAL[13]
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH[13]

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM[14]

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

The Drug Resistance Index (DRI)

The Drug Resistance Index (DRI) is a composite measure that combines the ability of antibiotics to treat infections with the extent of their use in clinical practice.[16] Described by *Science Magazine* as a Dow Jones for Drug Resistance, the DRI provides an aggregate trend measure of the effectiveness of available drugs, to track the usage and stock market values.[17]

The DRI can be calculated at the country, region, state, or even hospital level.[18] Country-level DRI estimates were recently published in BMJ Global Health for a subset of countries for a single year to demonstrate the power of the DRI to communicate problems with resistance.[19] Here we present the data with additional countries and years for which we have gathered enough data to calculate a composite DRI. The results underscore the urgent challenges facing the globe as DRI values are high in many countries especially in India, particularly many low- and middle-income countries.[20] In the highly connected world in which we live, the disparity in efficacy is a threat to global public health as resistant pathogens can rapidly spread between countries.[21] The DRI can also be applied to national and regional data.

Antibiotics used trends in india(ddd) (2000-2010)
Table 1: This table represents the antibiotics used trends in India from the year 2000 to 2010.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Aminoglycosides	80	73	55	48	63	85	109	128	195	208	179
Broad spectrum penicillins	691	633	633	636	575	565	676	728	738	793	848
Glycopeptides	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Cephalosporins	330	325	73	397	477	375	572	720	794	991	1178
Fluoroquinolones	492	469	572	614	584	936	1033	993	1014	1008	1019
narrow spectrum penicillins	52	44	35	35	37	21	20	20	20	23	24
Macrolides	247	237	284	285	273	234	264	287	307	359	405
Carbapenams	0	0	<1	<1	<1	<1	<1	<1	<1	<1	2

Antibiotic used trnds in india (2011-2018)
Table 2: This table represents the antibiotics used trends in India from the year 2011 to 2018.

	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycosides	172	156	145	125	119	125	-	-
Broad spectrum penicillins	908	939	950	1018	1055	-	-	-
Glycopeptides	<1	<1	<1	<1	<1	-	-	-
Cephalosporins	1414	1584	1678	1752	1822	-	-	-
Fluoroquinolones	942	884	792	753	762	-	-	-
Narrow spectrum penicillins	24	23	23	20	20	-	-	-
Macrolides	425	431	430	451	469	-	-	-
Carbopenams	2	<1	3	4	5	-	-	-

Resistance pattern for selected antibiotics[1]
1.   Staphylococus aureus[1]
Table 3: This table represents the resistance pattern of *staphylococus aureus* from the year 2008 to 2018.

Resistance antibiotics	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycosides	24%	36%	53%	44%	47%	45%	46%	-	32.3%	40.7%	
Fluoroquinolones	39%	66%	87%	73%	83%	81%	85%	-	71.4%	55%	75%
Glycopeptides	0%	0%	1%	1%	2%	0%	2%	1%	-	-	-
Narrow spectrum penicillins	13%	29%	49%	41%	53%	40%	42%	39%	-	-	-
Cephalosporins	56%	37%	46%	39%	69%	-	-	-	73%	-	100%
Linezolid	13%	-	-	-	-	-	-			0,3%	-

Beta lactams	-	-	-	-	-	-	-	-	76.6%	-	100%
Lincosamides	-	-	-	-	-	-	-	-	27.4%	-	-
Mupirocin	-	-	-	-	-	-	-	-	-	2%	-
Methicillin	-	-	-	-	-	-	-	-	-	-	100%
Ampicillin	-	-	-	-	-	-	-	-	-	-	75%

2. Enterococcus faecalis.[1]
Table 4: This table represents the resistance pattern of Enterococcus faecalis from the year 2008 to 2018.

Resistance antibiotics	2012	2013	2014	2015	2016	2017	2018
Aminopenicillins	13%	12%	16%	49%	41%	29.8%	
Fluoroquinolones	84%	79%	89%	-	-	80%	
Liezolid	0%	0%	5%	-	-	1.2%	
Vancomycin	0%	0%	6%	7%	-	2.8%	
Aminoglycosides	0%	0%	0%	0%	60%	39.8%	60.2%

3. *Streptococcus pneumoniae*[1]

Resistance antibiotocs	2015
Macrolides	32%
Penicillins	3%

4. *Enterobacter aerogens/clocae*[1]

Resistance antibiotics	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycosides	59%	64%	52%	55%	66%	50%	-	-	-
Carbapenams	23%	29%	36%	26%	43%	46%	-	26%	-
Cephalosporins	88%	90%	83%	80%	77%	78%	62%	68%	67%
Fluoroquinolones	72%	63%	59%	60%	64%	53%	37%	27%	40%
Piperacillin- tazobactem	75%	63%	63%	67%	64%	55%	-	24%	-
Glycylcyclines	-	-	12%	5%	0%	5%	-	-	-
Polymixins	-	-	-	6%	0%	1%	-	-	-
Amikacin	-	-	-	-	-	-	-	-	27%
Colistin	-	-	-	-	-	-	-	-	1.7%

5. *Salmonella typhi*[1]

Resistance antibiotics	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Amino glycosides	14%	12%	8%	8%	12%	13%	12%	-	-	-	-
Amino penicillins	13%	11%	8%	8%	5%	9%	4%	5%	0%	7.6%	4%
Amoxicillin clavulanate	2%	3%	0%	1%	3%	1%	3%	-	-	-	-
Cephalosporin s	3%	4%	2%	1%	2%	1%	2%	0%	2%	-	-
Fluoro quinolones	1%	19%	28%	37%	27%	27%	29%	68%	99%	73.3%	-
Piperacillin tazobactem	4%	1%	1%	1%	2%	1%	3%	-	-	-	-
Trimethoprim sulpha-methazole	17%	16%	9%	9%	4%	9%	2%	5%	-	-	-

6. *Pseudomonas aeroginosa*[1]

Resistance antibiotocs	2009	2010	2011	2012	2013	2014	2015	2016	2017
Amikacin	60%	64%	58%	45%	46%	39%	34%	37%	32%
Aminoglycosides	58%	72%	65%	54%	57%	58%	59%	41%	33%
Carbapenems	55%	52%	41%	49%	50%	47%	43%	41%	30%
Cefatazidine	78%	90%	78%	69%	65%	69%	42%	51%	33%
Fluoroquinolones	55%	68%	58%	54%	55%	55%	51%	44%	34%
Piperacillin tazobactem	25%	48%	35%	41%	57%	64%	31%	41%	22%
Polymixins				4%	2%	0%	2%	4%	4%

7. *Acinetobacter baumannii*[1]

Resstance antibiotics	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycosides	81%	91%	92%	92%	97%	86%	90%	74%	81%	75%	76.9%
Carbapenems	81%	87%	81%	85%	92%	87%	84%	73%	83%	77%	81.9%
Ceftazidime	88%	-	90%	93%	97%	87%	87%	83%	91%	84%	86.8%

Fluoroquinolones	88%	91%	91%	93%	95%	84%	84%	73%	80%	58%	84.9%
Amikacin (iv only)	-	89%	86%	81%	93%	82%	80%	71%	83%	75%	76.9%
Polymixins	-	-	-	-	-	-	3%	1%	1%	-	-
Piperacillin tazobactem	-	-	-	-	-	-	-	-	-	-	83.1%

8. Drug resistance index in india[1]

Year	DRI
2009	79%
2010	81%
2011	83%
2012	81%
2013	79%
2014	80%
2015	71%
MAX	71%

CONCLUSION
Inappropriate antibiotic use is a huge problem in India, and many bacteria were resistant to commonly used antibiotics and similarly, multidrug-resistant bacterial strains are numerous. Appropriate antibiotic use should be ensured by prohibiting over-the-counter sale of antibiotics and strengthening antimicrobial stewardship. The urgency at the policy level needs to translate into action on the ground, which won't happen until healthcare, pharmaceutical and livestock sector is better regulated.

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